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EIGHT YEARS AFTER JESSE'S DEATH, ARE HUMAN RESEARCH SUBJECTS ANY SAFER?

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It has been more than eight years since Jesse Gelsinger, Paul's son, died in a gene therapy clinical trial. But despite the press exposure and public outcry that followed, no progress has been made in fixing the broken system of protections for human research subjects. These people are no safer today than they were eight years ago—they are still at serious risk of exploitation and harm.

Many things stand in the way of better protection, but perhaps the greatest obstacle is the lack of adequate federal oversight. Not all human research is subject to federal regulations, since the regulations apply only to studies that are federally funded or that involve new drugs and devices for which applications have been filed with the Food and Drug Administration. An estimated 30 percent of studies are not covered. In contrast, each and every experiment involving animals is regulated by the federal government under the Animal Welfare Act.

Further, the federal oversight that does exist offers minimal protection. Last year, a report by the inspector general of the Department of Health and Human Services found that the FDA, the agency responsible for overseeing most clinical trials, inspected just 1 percent of study sites. Small wonder, since it has a mere two hundred investigators and there are 350,000 sites.¹ When the FDA detects a problem, it typically does so long after the research is completed. Proactive oversight of the safety of human subjects is extremely limited.

Paul Gelsinger and Adil E. Shamoo, "Eight Years after Jesse's Death, Are Human Research Subjects Any Safer?" *Hastings Center Report* 38, no. 2 (2008): 25-27.

Given the lack of oversight, it is no surprise that adverse events are underreported. According to the only comprehensive study on the subject, just eight deaths and 386 adverse events were reported to the Office of Human Research Protections of the Department of Health and Human Services from 1990 to 2000. Yet we would have expected several hundred deaths and tens of thousands of adverse events in a ten year period.²

Paul Gelsinger gained an intimate understanding of the underreporting of adverse events after his son died. Jesse, who was eighteen years old, was participating in a phase I safety study of a gene transfer therapy for ornithine transcarbamylase deficiency (OTCD), a rare metabolic condition. He had a mild form of the disorder and knew that he would get no medical benefit from the trial. But he enrolled in the study, which was conducted at the University of Pennsylvania, because it seemed safe enough. The consent form did not mention any serious reactions in humans, and conversations with the doctors led Paul and Jesse to believe the therapy was safe. And the trial could possibly benefit people with severe forms of OTCD. Paul encouraged his son to participate.

As it happened, Jesse received the maximum dose of the gene transfer infusion. Within a day, he experienced a massive immune response to the adenoviral vector. Four days later, on September 17, 1999, he had multiple organ failure and died. Paul set out to discover what had gone wrong. He confronted the doctors involved in the study. Meanwhile, Adil Shamoo and members of his organization, Citizens for Responsible Care and Research, a nonprofit dedicated to improving the protection of humans in research, were also asking questions. Two months after Jesse's death, Paul and CIRCARE learned that the FDA had not created a system for tracking gene therapy patients and disseminating information about serious adverse reactions. Further digging led to the minutes of a 1995 meeting of the Recombinant DNA Advisory Committee of the National Institutes of Health, which oversees gene therapy research. In the minutes, an FDA representative admitted under pressure that one reason that the FDA did not create this tracking system was that his superiors "answer to industry."³ The drug companies were using their influence with the FDA to prevent the dissemination of adverse reaction information on the grounds that it was proprietary. It did not seem to matter that withholding this information endangered the lives of those participating in research.

The FDA's own investigation into Jesse's death found that the researchers were responsible because they had violated the study's protocol in multiple ways. They failed to obtain proper informed consent. They made false statements to the FDA

and the institutional review boards charged with oversight of the research. They did not halt the study, as required, after subjects developed various toxic reactions.

What the FDA investigation neglected to mention is that the agency itself had some of this data a year before Jesse participated in the trial, yet it allowed the trial to continue and did not disseminate the data. Eventually, we found that there had been nearly seven hundred adverse reactions associated with adenoviral gene transfer procedures before Jesse's death. Fewer than 6 percent of these reactions had been appropriately reported to the RAC, but 95 percent of them had been reported to the FDA.

There were other problems. The University of Pennsylvania's IRB was unable to conduct adequate continuing review of protocols, largely because it was

understaffed. In addition, its membership consisted primarily of Penn employees and therefore may have been biased in favor of the university's research.

Financial conflicts of interest were also uncovered. The principal investigator owned a 30 percent interest in the investigational gene therapy and technology, and the University of Pennsylvania owned stock in the company tied to the gene therapy. There was a single sentence in the consent form suggesting that the principal investigator and the University of Pennsylvania could benefit financially from the outcome of the trial, but that sentence in no way described the nature or extent of the financial conflicts of interest.

The federal government charged the researchers and their institutions with fraud. The defendants entered into settlement agreements involving fines and other penalties. But there was no acknowledgment of responsibility, let alone wrongdoing, nor was there even a hint of remorse in the form of an apology.⁴ Since then, Paul and CIRCARE have been working to promote federal legislation to safeguard research participants. Called the National Human Subjects Research Act, it would require education and training for all investigators involved in clinical trials, reporting of all adverse events to a central national office, and strict management of conflicts of interest. It would also require that the majority of an IRB's members come from research institutions other than the ones involved in a study. Unfortunately, bills submitted to the Senate and the House of Representatives are languishing in committees. No hearings have been held to discuss them.

Small reforms have occurred. For example, IRBs today would be reluctant to approve a study in which subjects with schizophrenia were suddenly withdrawn from their medication, causing a relapse. It is also unlikely that IRBs would approve a study in which human subjects were given a substance to induce psychosis. Only a decade ago, such experiments were allowed to proceed. Another reform came eighteen months after Jesse's death, when the National Institutes of Health and the FDA finally put in place a system for reporting adverse reactions. The FDA representative who made the "my superiors answer to industry" statement told Paul and his attorney, Alan Milstein, that Jesse would still be alive if the system had been enacted before he entered the clinical trial, as it should have been.

But this is very limited progress, and without strong national legislation, there are no guarantees that the ethical gains will be maintained. We will keep fighting to repair this broken system of protections for human subjects, but our greatest fear is that other preventable deaths and serious adverse events will occur before the system is adequately reformed.

1. Department of Health and Human Services, Office of Inspector General, "The Food and Drug Administration's Oversight of Clinical Trials," OEI-01-06-00160, September 2007, <http://www.oig.hhs.gov/oei/reports/oei-01-06-00160.pdf>; A.E. Shamoo, ed., *Ethics in Neurobiological Research with Human Subjects* (Amsterdam, The Netherlands: Gordon and Breach, 1997).

2. For details, see A.E. Shamoo, "Adverse Events Reporting: The Tip of an Iceberg," *Accountability in Research* 8 (2001): 197-218.

3. Minutes of the National Institutes of Health Recombinant DNA Advisory Committee Meeting, June 8–9, 1995, 12; <http://www4.od.nih.gov/oba/rac/minutes/6-8-9-95.pdf>.

4. United States Department of Justice, "U.S. Settles Case of Gene Therapy Study That Ended with Teen's Death," February 9, 2005; <http://www.usdoj.gov/usao/pae/News/Pr/2005/feb/UofPSettlementpercent20release.html>. [JANPT # 67 Gelsinger Shamoo Essay HCR April 08.pdf](#)